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A previously undescribed cutaneous paraneoplastic syndrome in a cat with thymoma

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1 **Abstract**

2 **Background**– Exfoliative dermatitis is a well-recognized cutaneous paraneoplastic
3 syndrome (PNS) associated with thymoma in cats, of which the clinical and
4 histopathological presentation has been well characterized.

5 **Objectives** – To describe a novel clinical skin manifestation associated with
6 thymoma in a cat

7 **Animal** – A 14-year-old neutered female domestic short haired cat

8 **Methods** – Physical, abdominal ultrasonographic, thoracic radiographic,
9 ultrasonographic and computed tomographic examinations, histopathologic
10 assessment of the skin and mediastinal mass.

11 **Results** – The cat was presented with non-inflammatory alopecia, with a dorsal
12 multifocal distribution. Examination of the alopecic areas using a dermascope
13 indicated an apparent lack of follicular ostia. Histopathological assessment of
14 alopecic areas confirmed follicular and epidermal atrophy, trichilemmal keratinization
15 and mild orthokeratotic hyperkeratosis. Diagnostic imaging revealed a mediastinal
16 mass, which was surgically removed. Histopathological and immunohistopathological
17 examination of the mass was consistent with a thymoma, associated with
18 multiloculated cyst formation and multifocal cholesterol granulomas. Following
19 surgery, hair re-growth was noted in the previously alopecic areas. The cat was
20 euthanized 3.5 months later because of recurrent chylothorax, suspected to be a
21 post-operative complication. The alopecic lesions had markedly improved.

22 **Conclusions and clinical importance** – Thymoma-associated PNS might not
23 always manifest as an exfoliative dermatitis, and should be considered in the
24 differential diagnosis of multifocal non-inflammatory alopecia.

25 A 14-year old neutered female domestic shorthair cat was presented for
26 investigation of alopecic patches of skin on the back that the owner noticed the day
27 before presentation. The cat showed no signs of pruritus nor over-grooming. In
28 hindsight, the owner reported that the cat had developed progressive lethargy over
29 the previous 9 months. The cat lived strictly indoors without any other pets and was
30 fed a complete diet. The last vaccine was given 2 years prior to presentation, and
31 regular antiparasitic treatment was not administered.

32 General physical examination was unremarkable. Dermatological examination
33 showed multifocal small, well demarcated, areas of hair loss over the dorsum,
34 extending from 0.5 cm to 3 cm in diameter. The areas showed no evidence of
35 inflammation, and the skin had a slightly shiny appearance (Figure 1.a). Throughout
36 the hair coat there was fine scale and the hair was slightly greasy to touch.
37 Dermoscopic assessment of the alopecic areas showed fewer follicular ostia than
38 expected in the area and compared to surrounding skin, suggesting a loss of some
39 follicles. The main differential diagnoses considered included immune-mediated
40 follicular diseases such as pseudopelade and alopecia areata, endocrine diseases
41 such as hyperadrenocorticism and hypothyroidism, demodicosis, dermatophytosis
42 and a paraneoplastic syndrome (PNS).

43 A complete blood count and serum biochemistry panel including serum
44 thyroxin concentration did not reveal any significant abnormalities. Trichograms,
45 deep skin scraping, Wood's lamp test, and a fungal culture were normal or negative.
46 Skin biopsy samples of the alopecic lesions were performed. On histopathological
47 assessment, the epidermis was thinner than normal, consistent with atrophy. There
48 was mild to moderate orthokeratotic hyperkeratosis, with very mild segmental
49 parakeratosis around the ostia of the hair follicles. Most hair follicles were atrophic
50 and in telogen phase of the growth cycle, with absent or small and distorted hair
51 shafts. Trichilemmal keratinization was also present (Figure 2). These histological
52 findings were not characteristic of any differentials considered, and a medical
53 evaluation was pursued.

54 On abdominal ultrasound, a few well-defined hyperechoic splenic nodules
55 were considered typical of myelolipomas. Thoracic radiographs revealed a cranio-
56 ventral mediastinal mass (Figure 3), which was also noted on thoracic ultrasound.
57 Ultrasound-guided fine-needle aspirates of the mediastinal mass were performed.
58 Cytology was compatible with a thymoma, although a definitive diagnosis could not
59 be reached. A pre-operative computed tomographic examination of the thorax did
60 not reveal any sign of infiltration, vascular invasion or metastasis.

61
62 A median sternotomy was performed. A 5 cm x 3 cm x 3 cm cranial
63 mediastinal mass was extirpated, and the sternal lymph node was removed. Most of
64 the centre of the mass comprised a multiloculated cyst like cavity lined by slender
65 trabeculae of fibrovascular connective tissue. Cystic spaces were approximately
66 1cm in diameter, sometimes slightly larger. Some pre-existing thymic structure was
67 evident, with a capsule, cortex, medulla and Hassall's corpuscles was noted.
68 However, the distinction between cortex and medulla was ill-defined and the
69 parenchyma was expanded by a population of lymphoid cells (predominantly small),

70 numerous tingible body macrophages, and an increased number of plump oval
71 epithelial cells with approximately 1-2 mitotic figures per high-power field (400X
72 magnification). Multiple cholesterol granulomas were also present.
73 Immunohistochemically, a diffuse and strong CD3 and pan-cytokeratin (CK) labelling
74 was present throughout the parenchyma, and small numbers of scattered Pax5
75 positive cells were noted. The lining of the cystic spaces also included CD3 and CK
76 positive cells but no ciliated epithelial cells were evident. Based on the 2015 World
77 Health Organization (WHO) human classification of tumors of the thymus, the
78 histopathological findings were consistent with a type B2 thymoma.¹ Some clusters
79 of epithelial cells had breached the capsule, but no metastasis was detected within
80 the sternal lymph node. The clinical and histopathological findings were consistent
81 with a stage IIa thymoma, based on the Masaoka-Koga human staging system.² It
82 was suspected that the multifocal alopecia was a PNS associated with the thymoma,
83 although these features have never been reported previously.

84 The cat was discharged from the hospital three days after the surgery. Three
85 weeks later (day 25), the demeanor of the cat had improved. Physical examination
86 was unremarkable, except for unchanged alopecic patches on the dorsum. Thoracic
87 radiographs and ultrasound revealed a moderate amount of bilateral pleural effusion,
88 which was drained. Fluid analysis was consistent with a chylous effusion, and was
89 suspected to be a post-operative complication. A month later (day 58), the hair was
90 regrowing on the dorsum (Figure 1.b), supporting the diagnosis of thymoma-
91 associated cutaneous PNS. Although the pleural effusion initially resolved, the cat
92 was presented a month later (day 87) with a moderate expiratory dyspnea.
93 Recurrence of the bilateral pleural effusion was confirmed and the thoracic cavity
94 drained. The cat was presented again two weeks later (day 103) for progressive
95 dysorexia and lethargy, and an acute onset of dyspnea. A second recurrence of the
96 pleural effusion was confirmed and the cat was euthanized. Necropsy was declined
97 by the owners.

98 Discussion

99 Thymic epithelial tumors represent a complex group of neoplastic diseases,
100 with variable clinical behavior and histopathological appearance.^{1,3-5} Their
101 classification is controversial in humans, and the WHO classification of thymic
102 tumors aimed to unify the previous systems.¹ Cystic thymomas have previously been
103 described in cats,⁶ but the cystic spaces were unusually large in our case. This was
104 reminiscent of the cystic degeneration commonly described in humans, which may
105 be mistaken for a non-neoplastic thymic cyst.⁷

106 Cats with thymoma often present with respiratory signs,^{4,5 6,7} however, skin
107 lesions are occasionally the presenting complaint.^{8,9} Multiple cases of thymoma-
108 associated cutaneous PNS have been reported, and the clinical presentations were
109 all consistent with exfoliative dermatitis.^{8,9} Cats typically present with generalized
110 desquamation, alopecia, crusting, scaling, and sometimes erythema. The lesions
111 usually start on the head, but progressively become generally distributed in an
112 asymmetrical pattern. Histopathological features include orthokeratotic and

113 parakeratotic hyperkeratosis with extensive desquamation. In the epidermis and
114 follicular infundibula, there are variable degrees of keratinocyte apoptosis, CD3+
115 lymphocytic exocytosis, and hydropic degeneration of basal cells (interface
116 dermatitis). Follicular changes can extend to infiltrative mural folliculitis, with only a
117 few or no remaining sebaceous glands.^{8,9} The pathophysiology is not clearly
118 understood, but it is suspected that autoreactive cytotoxic T-cells activated by the
119 abnormal thymus could aberrantly target epithelial cells.⁹ The clinical and
120 histopathological presentation of the cat in this report did not correlate with the
121 exfoliative dermatitis typically reported in cats with thymoma.

122 Although uncommon in humans, thymoma-associated cutaneous PNS have
123 been reported. Reported dermatological changes are characteristic of alopecia
124 areata or paraneoplastic pemphigus.^{10,11} Alopecia areata is a non-scarring
125 inflammatory alopecic disease with no overt epidermal changes. It is a clinical entity
126 that manifests as patchy areas of hair loss on the scalp and other parts of the body.
127 It is suspected to be an autoimmune disease that results from selective T-cell
128 mediated damage to anagen follicles.^{11,12} The histopathologic appearance varies
129 depending on disease duration.^{11,12} Based on the clinical presentation of the cat,
130 alopecia areata was considered, but not supported by the histopathological
131 appearance of the skin. Based on the history, the alopecic patches had developed
132 recently and no bulbitis could be seen histologically to suggest any underlying
133 alopecia areata. Although a late stage alopecia areata could still be considered, the
134 lack of inflammatory infiltrate in the histological sections was less consistent with this
135 disease. Paraneoplastic pemphigus is an immune-mediated blistering disorder
136 characterized by vesicobullous changes affecting the head, trunk and extremities.
137 Erythema and inflammation are always associated with maculae, papules and
138 plaques, and oral erosive lesions are often severe. Acantholysis, keratinocyte
139 necrosis, and vacuolar interface dermatitis are typical histopathological features. The
140 clinical and histopathological presentation of the cat herein was not consistent with
141 this PNS.

142 Feline paraneoplastic alopecia is another cutaneous PNS that has been
143 associated with pancreatic and biliary carcinomas.⁸ Hair loss is typically symmetrical,
144 starts over the ventrum, but can progress to the head and extremities. The alopecic
145 skin is often shiny and thin. Foot pads are often dry, crusted and fissured when
146 involved.⁸ On histopathology, marked follicular telogenization, miniaturization and
147 atrophy are characteristic. Other findings include mild epidermal acanthosis and
148 hyperplasia, and patchy parakeratosis with a mild perivascular, mainly mononuclear,
149 inflammatory dermal infiltrate.⁸ Follicular telogenization and atrophy were also noted
150 in this case. However, the distribution of the lesions was very different from the
151 typical feline paraneoplastic alopecia, and there was no mononuclear inflammatory
152 infiltrate in the dermis.

153 In conclusion, we report a presumptive thymoma-associated cutaneous PNS, for
154 which the clinical and histopathological presentation is not entirely consistent with
155 previously reported PNS in cats or other species.

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157

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189 **Figures captions**

190 **Figure 1.** Feline thymoma: Multifocal non-inflammatory alopecia, with dorsal
191 distribution.

192 Close-up of the largest alopecic patch located on the mid-dorsum at the initial visit
193 (day 0). (b) Follow-up after the surgery showing re-growing shorter hairs in an area
194 of previous hair loss (day 58).

195 **Figure 2.** Feline thymoma: Histopathological features of the skin (alopecic area over
196 the dorsum).

197 The epidermis is composed of only one to two layers of cells, consistent with
198 epidermal atrophy (black arrowhead). There is mild to moderate orthokeratotic
199 hyperkeratosis (black asterisk). Most hair follicles are atrophic and in telogen phase
200 of the growth cycle (black arrow), with hyalinisation of keratin consistent with
201 trichilemmal keratinisation (white arrowhead); Haematoxylin and eosin (H&E).

202 **Figure 3.** Feline thymoma: Thoracic radiographic features

203 Ill-defined rounded soft tissue mass extending from the thoracic inlet to the 4th
204 intercostal space, associated with marked dorsal displacement of the thoracic
205 trachea; left latero-lateral view.